

Characteristics of patients with severe asthma who experienced treatment failure with omalizumab

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ABSTRACT

Background: Omalizumab, an anti-IgE antibody, has been widely used in many countries, including Japan. However, some patients do not respond to omalizumab, and the cause of treatment failure has not been fully elucidated.

Objective: This study aimed to evaluate the characteristics of adult asthma patients who failed to achieve disease control with omalizumab in a real-world setting.

Methods: We retrospectively reviewed the medical records of patients in Tokyo Women's Medical University Hospital between March 2009 and May 2016. The patient characteristics and factors for treatment failure with omalizumab were evaluated, as were treatment alternatives after discontinuation of omalizumab.

Results: In total, 59 patients were included in this study. The omalizumab-ineffective group had a significantly higher number of patients with eosinophilic sinusitis ($P = 0.001$) and eosinophilic otitis media ($P = 0.023$) than the omalizumab-effective group. A multivariate analysis revealed that both eosinophilic chronic rhinosinusitis (odds ratio: 23.4; $P = 0.011$) and eosinophilic otitis media (odds ratio: 6.71; $P = 0.039$) were associated with treatment failure with omalizumab. Most patients with eosinophilic comorbidities of the ear, nose, and throat (ENT) in the omalizumab-ineffective group received mepolizumab or benralizumab as alternative therapy, following which disease control was achieved.

Conclusion: Eosinophilic comorbidities of the ENT may affect treatment failure with omalizumab in patients with severe asthma. Anti-interleukin-5 antibody or anti-interleukin-5R α antibody rather than anti-IgE antibody should be considered as an additional therapy for patients with severe asthma who have eosinophilic comorbidities of the ENT.

1. Introduction

Asthma is a heterogeneous airway inflammatory disease affecting 300 million people worldwide. Most patients with asthma achieve disease control with a combination of inhaled corticosteroids and regular asthma therapy, including a long-acting β_2 agonist (LABA), leukotriene receptor antagonist (LTRA), and long-acting muscarinic antagonist (LAMA). However, in 5%–10% of patients with asthma, the condition remains uncontrolled despite administration of a combination therapy and is associated with significant morbidity and mortality [1]. In addition to regular asthma therapy, patients with severe asthma may also

receive oral corticosteroids (OCS) or molecular-targeted biologic drugs or undergo bronchial thermoplasty (BT) [2].

Omalizumab is a monoclonal IgE antibody that was approved in 2009 and is widely used in Japan. This drug specifically binds to the circulating IgE and blocks the inflammatory cascade [3]. Via these mechanisms, it can reduce the rate of asthma exacerbation and use of OCS [4–7]. Predictive factors associated with a greater treatment efficacy are fractional exhaled nitric oxide (FeNO) levels, peripheral blood eosinophil counts, and serum periostin levels, but not total IgE levels [8–10]. Not all patients respond to omalizumab, and the cause of treatment failure is undetermined. Therefore, our study aimed to evaluate the characteristics of adult asthma patients who were treated with

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Abbreviations

ENT	ear, nose, and throat
LABA	long-acting β_2 agonist
LTRA	leukotriene receptor antagonist
LAMA	long-acting muscarinic antagonist
OCS	oral corticosteroids
BT	bronchial thermoplasty
FeNO	fractional exhaled nitric oxide
BMI	body mass index
ECRS	eosinophilic chronic rhinosinusitis
EOM	eosinophilic otitis media
GETE	global evaluation of treatment effectiveness
OR	odds ratio
CI	confidence interval
IL	interleukin

omalizumab but failed to achieve disease control in a real-world setting. To the best of our knowledge, our study is the first to evaluate the factors related to treatment failure with omalizumab.

2. Material and methods

2.1. Study population

We retrospectively reviewed the medical records of patients between March 2009 and May 2016 at Tokyo Women's Medical University Hospital where biologic drugs are widely used for asthma treatment. During this observation period, omalizumab was the only available biologic drug for severe asthma in Japan. We collected patients who received omalizumab during this period. The inclusion criteria of this study were as follows: 1) age 18 years or above, 2) positivity to at least one perennial allergen confirmed via a blood test or prick test, 3) severe persistent asthma requiring regular treatment with >1000 $\mu\text{g}/\text{day}$ of beclomethasone dipropionate or equivalent, LABA, and other additional asthma medications, such as OCS, LTRA, LAMA, theophylline, and antihistamine (equivalent to guideline steps 4 or 5, GINA 2019), 4) patients with conditions considered by physicians as an indication for biologic therapy, and 5) patients who received omalizumab at least 16 weeks. The exclusion criteria included 1) use of an investigational new drug, 2) history of malignancy, 3) idiopathic eosinophilia or eosinophilia caused by a parasite infection, 4) acquired or congenital immunodeficiency, and 5) discontinuation of omalizumab within 16 weeks. The institutional review board of Tokyo Women's Medical University approved the study (approval number: 5593), and it was performed in accordance with the Good Clinical Practice and Declaration of Helsinki. Written informed consent was obtained from the patients.

2.2. Data collection

We identified treatment failure based on global evaluation of treatment effectiveness (GETE) at 16 weeks. The physician's GETE score evaluates multiple aspects to determine the response to omalizumab based on interviews, severity of symptoms, usage of medication and spirometry examinations [11]. The GETE score is a five-point scale dividing patients according to asthma symptoms into: excellent, good, moderate, poor, or worsening of symptoms. The omalizumab-effective group was defined as patients with excellent or good symptom management, while the omalizumab-ineffective group was defined as patients with moderate, poor, or worsening symptoms.

We evaluated patient characteristics, including age, sex, treatment duration, disease comorbidity, smoking status, eosinophil count, total IgE level, body mass index (BMI), FeNO level, and use of OCS. Regarding

ENT comorbidities, a skilled otolaryngologist diagnosed patients with eosinophilic chronic rhinosinusitis (ECRS) and eosinophilic otitis media (EOM) based on the diagnostic criteria. Briefly, the diagnosis of ECRS is done based on several categories including bilateral disease sites, nasal polyps, CT findings, and eosinophilia in peripheral blood [12]. The total clinical score (i.e., JESREC score) was calculated according to each individual score, and the cutoff value for the JESREC score for ECRS was 11. If the JESREC score was 11 or higher, the patient was diagnosed with ECRS. EOM is characterized by a high-viscosity middle ear effusion containing eosinophils [13].

The characteristics of patients were compared between the omalizumab-effective group and the omalizumab-ineffective group. Moreover, the factors associated with treatment failure with omalizumab were evaluated, and the outcome of patients who received alternative treatment after discontinuation of omalizumab was examined. The characteristics of patients, type of treatment, effect of alternative treatment, and side effects (if applicable) were assessed by reviewing the medical records.

2.3. Statistical analysis

Data for continuous variables were expressed as median (interquartile range) and for categorical variables as number (percentage). Continuous variables were compared using the Mann-Whitney *U* test and the categorical variables with the Fisher's exact test. To determine the factors associated with treatment failure with omalizumab, a univariate logistic regression analysis was performed. Afterward, a multivariate logistic regression analysis was conducted using significant variables with *P* values < 0.20 in the univariate analysis. A *P* value < 0.05 was considered statistically significant. Analyses were performed using the JMP software v11.0 (SAS Institute Japan Ltd., Tokyo, Japan).

3. Results

3.1. Characteristics of the patients

In total, 65 patients received omalizumab during this study period. Among them, five patients were excluded owing to side effects and one patient discontinued due to carcinogenesis within 16 weeks. Fifty-nine patients were finally included in the analysis (Fig. 1). The median (interquartile range) age of the participants was 52 (range: 43–65) years, and 20 (34%) patients were men (Table 1). The median treatment duration was 53 (range: 24–83) weeks. Thirty-nine (66%) patients used OCS at the initiation of omalizumab, and only two (3.4%) patients were current smokers.

3.2. Comparison between the omalizumab-effective and ineffective groups

The symptoms of 39 patients improved after the initiation of omalizumab (GETE: excellent 22/good 17), while 20 patients did not achieve disease control with omalizumab (moderate 9/poor 9/worsening 2) (Table 2). The omalizumab-ineffective group had a significantly higher number of patients with ECRS ($P = 0.001$) and EOM ($P = 0.023$) than the omalizumab-effective group. The duration of omalizumab therapy was significantly longer in the omalizumab-effective group than in the omalizumab-ineffective group ($P < 0.001$). The number of male patients, with current use of OCS, BMI, blood eosinophil counts, total IgE level, FeNO level, and other comorbidities did not significantly differ between the two groups.

3.3. Predictor of treatment failure with omalizumab

The univariate analysis of the association between the measured parameters and omalizumab failure showed that ECRS (odds ratio [OR]: 20.5, 95% confidence interval [CI]: 2.29–182; $P = 0.007$) and EOM (OR: 6.46, 95% CI: 1.45–28.8; $P = 0.014$) were predictors of treatment failure

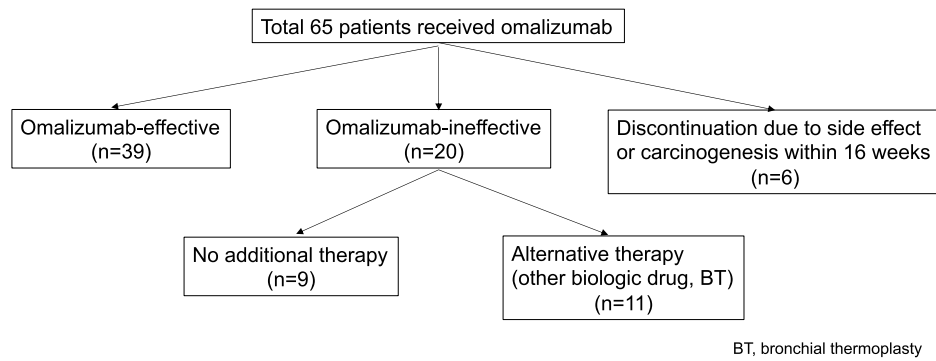


Fig. 1. A flow chart of participants and the number of patients included in each group.

Table 1
Patients characteristics included in this study.

Characteristics	Overall patients (n = 59)
Age (years)	52 (43–65)
Sex (male)	20 (34)
BMI (kg/m ²)	22.8 (20.3–25.8)
Smoking status	
Never	37 (62.7)
Former	20 (33.9)
Current	2 (3.4)
Treatment duration (month)	53 (24–83)
Eosinophil (/μL)	229 (79–518)
Total IgE (IU/mL)	208 (88.6–392)
FeNO (ppb)	28 (18–70.5)
OCS use	39 (66)

Values are median (interquartile range) or number (%).

Table 2
Patient characteristics in omalizumab effective and ineffective group before omalizumab treatment.

Characteristics	Omalizumab-effective (n = 39)	Omalizumab-ineffective (n = 20)	P
The GETE score	excellent 22/good 17	moderate 9/poor 9/worsening 2	N/A
Age (years)	51 (43–64)	55 (43–65)	0.659
Sex (male)	11 (28)	10 (50)	0.151
BMI (kg/m ²)	22.8 (20.7–25.6)	23.2 (20.1–26.2)	0.792
Smoking			
Never	25 (64.1)	12 (60)	0.78
Former	12 (30.7)	8 (40)	0.66
Current	2 (5.1)	0 (0)	0.54
Treatment duration (month)	71 (44–86)	25.5 (7–44.5)	<0.001
Eosinophil (/μL)	163 (60–518)	319 (140.5–512)	0.176
Eosinophil >300/μL	15 (38.5)	12 (60)	0.168
Total IgE (IU/mL)	208 (95.9–408)	208 (75.6–351)	0.581
FeNO (ppb)	26 (18–63)	31 (18–75)	0.61
OCS use	23 (58.9)	16 (80)	0.149
Comorbidity			
Allergic rhinitis	21 (53.8)	7 (35)	0.27
Allergic conjunctivitis	1 (2.6)	0 (0)	0.98
Atopic dermatitis	2 (5.2)	1 (5)	0.77
ECRS	1 (2.6)	7 (35)	0.001
EOM	3 (7.8)	6 (30)	0.023
Idiopathic urticaria	2 (5.2)	1 (5)	0.78
ABPA	1 (2.6)	0 (0)	0.98
EGPA	0 (0)	1 (5)	0.21
COPD	5 (12.8)	2 (10)	0.98

Values are median (interquartile range) or number (%).

ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media; ABPA, allergic bronchial pulmonary aspergilloma.

EGPA, eosinophilic granulomatosis with polyangiitis.

with omalizumab (Table 3). Similarly, the multivariate analysis revealed that ECRS (OR: 23.4, 95% CI: 2.06–271; P = 0.011) and EOM (OR: 6.46, 95% CI: 1.51–39.2; P = 0.039) were the only factors associated with treatment failure with omalizumab.

3.4. Additional treatment

Of the 20 patients in the omalizumab-ineffective group, 11 received additional therapy such as other biologic drugs or BT (Table 4). Most patients in the omalizumab-ineffective group with eosinophilic comorbidities received mepolizumab or benralizumab as an additional therapy. Patients who received treatment with mepolizumab or benralizumab achieved disease control for both asthma and eosinophilic comorbidities (Table 5). In two patients who received dupilumab after mepolizumab, symptoms for both asthma and eosinophilic comorbidities decreased.

4. Discussion

This study investigated factors related to treatment failure with omalizumab in a real-world setting. The results showed that eosinophilic comorbidities of the ENT were associated with treatment failure with omalizumab. Parameters such as blood eosinophil counts, total IgE level, FeNO level, and other disease comorbidities did not affect treatment failure in this study. Furthermore, the patients with eosinophilic comorbidities of the ENT in the omalizumab-ineffective group achieved disease control with mepolizumab (anti-interleukin [IL]-5 antibody) or benralizumab (anti-IL-5Rα antibody).

Currently, there are many studies on predictive factors for the treatment efficacy of omalizumab. A randomized controlled trial has shown that severe asthma patients with a high blood eosinophil counts, FeNO, and serum periostin showed a significantly low exacerbation frequency [8]. Moreover, several studies have assessed the predictive factors of treatment efficacy. In this study, we evaluated physician's

Table 3
Association of measured parameters with omalizumab failure.

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age (years)	1.02	0.99–1.04	0.56			
Sex (male)	2.55	0.83–7.81	0.102	3.47	0.62–19.3	0.155
BMI (kg/m ²)	1.06	0.72–1.43	0.521			
Eosinophil >300/μL	2.4	0.80–7.23	0.12	1.89	0.71–9.13	0.19
Total IgE (IU/mL)	1	0.99–1.01	0.17	0.99	0.99–1.01	0.23
OCS use	2.78	0.78–9.89	0.114	4.07	0.63–26.3	0.14
Allergic rhinitis	0.46	0.15–1.40	0.173	0.41	0.16–1.31	0.17
ECRS	20.5	2.29–182	0.007	23.4	2.06–271	0.011
EOM	6.46	1.45–28.8	0.014	6.71	1.51–39.2	0.039

OR, odds ratio; CI, confidence interval.

ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media.

Table 4

Additional treatment after failure with omalizumab.

Additional treatment	Total (n = 11)
Mepolizumab	9
Benralizumab	3
Dupilumab	2
Bronchial thermoplasty	1

GETE score as marker of treatment effectiveness because the GETE at 16 weeks well predicted the persistency of response to omalizumab treatment [11]. Interestingly, our results showed that eosinophilic comorbidities of the ENT affected treatment failure with omalizumab. This result was consistent with previous reports, which showed the presence of nasal polyps was associated with poor asthma control and reducing omalizumab response [14–16]. Although blood eosinophil counts and FeNO, which tend to increase in ECRS and EOM, were not predictive factors in this study, there is a possibility that these parameters were affected by existing treatment such as OCS. As 80% of omalizumab-ineffective patients used OCS regularly at the initiation of omalizumab treatment, there is some risk of underestimating the difference between the two groups.

A previous study showed that treatment for eosinophilic comorbidities in asthma patients is sometimes challenging [11]. Omalizumab may partly improve Th2-type eosinophilic inflammation, and several reports showed the efficacy of omalizumab for both asthma and eosinophilic comorbidities [17,18]. However, as our study showed, eosinophilic inflammation in the upper airway could not be completely suppressed by this drug. It has been reported that the poor reduction of blood eosinophils after omalizumab treatment was associated with poor asthma control and lung function impairment [19,20]. Although we did not evaluate blood eosinophil counts in all patients after omalizumab treatment, it has possibility that prevalence of eosinophilic comorbidities, especially ECRS, contributes to persistence of eosinophilia and therefore poor response to omalizumab [14,19]. Most omalizumab-ineffective patients with eosinophilic comorbidity symptoms improved with anti-IL-5 or IL-5R α antibody. Our result was consistent with that of a previous report, which showed the efficacy of mepolizumab or reslizumab in patients with eosinophilic asthma after treatment failure with omalizumab [21,22]. A previous report revealed that mepolizumab can significantly improve the exacerbation rate and symptoms in patients with severe asthma who present with ECRS. Thus,

eosinophil-targeted therapy is effective in severe asthma patients with eosinophilic comorbidities [23]. As suggested by the “one airway, one disease” theory, adequate treatment of upper airway inflammation may improve lower airway inflammation [24–26].

Furthermore, dupilumab, a human anti-IL-4R α monoclonal antibody, was found to be effective in patients who experienced treatment failure with mepolizumab. Although the effect of dupilumab on eosinophilic ENT comorbidities has not been fully understood, several studies have shown that dupilumab is effective for the treatment of severe chronic rhinosinusitis with nasal polyps, which predominantly displays type 2 inflammatory signatures such as IL-4 and IL-13 [27,28]. Therefore, it can be a candidate for treating patients with severe asthma who present with eosinophilic comorbidities. Further studies with strict protocols must be conducted to validate this finding.

Our study has several limitations that should be acknowledged. First, because a single-center retrospective analysis was conducted in this study, the results might not be applicable to all patients. Second, the number of patients included in this study was relatively small. Therefore, it is possible that the small sample size reduced the power of this study and underestimated the difference between groups. However, we believe that the significance of eosinophilic comorbidities of the ENT is obvious and cannot be denied. Lastly, most participants received subsidies for asthma from the Tokyo metropolitan government. Thus, their treatment decision might have been biased. However, approximately 60% of patients with severe allergic asthma achieved disease control with omalizumab in this study, and this result was consistent with that of a previous large multicenter study [29]. Therefore, the characteristics of the patients in this study can be generalized.

5. Conclusions

In conclusion, the comorbidities of eosinophilic ENT disease may affect treatment failure with omalizumab in patients with severe asthma. Anti-IL-5 or anti-IL-5R α antibody, rather than anti-IgE antibody, should be considered as an additional therapy for patients with severe asthma who present with EOM or eosinophilic sinusitis/polypoid.

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Table 5

Treatment outcome of 11 patients who received additional therapy.

No.	Age	Sex	Comorbidity	Additional treatment①		Additional treatment②	
1	47	F	allergic rhinitis	mepolizumab	discontinuation due to side effect (skin lush)	dupilumab	effective
2	66	M	ECRS, allergic rhinitis	benralizumab	effective for both asthma and complication		
3	62	M	ECRS, EOM	mepolizumab	effective for both asthma and complication		
4	41	F	EOM	mepolizumab	effective for both asthma and complication		
5	40	F	EOM, allergic rhinitis, idiopathic urticaria	mepolizumab	discontinuation due to worsening of idiopathic urticaria	omalizumab	ineffective
6	66	F	EOM, EGPA	BT	effective		
7	67	M	ECRS, allergic rhinitis	mepolizumab	effective for both asthma and complication		
8	54	M	EOM, allergic rhinitis	mepolizumab	effective for both asthma and complication		
9	57	F	ECRS, allergic rhinitis, idiopathic urticaria	mepolizumab	ineffective	benralizumab	effective for both asthma and complication
10	62	M	ECRS, EOM	mepolizumab	once improved symptoms then gradually worsened	dupilumab	effective for both asthma and complication
11	41	M	ECRS, EOM, allergic rhinitis	mepolizumab	once improved symptoms then gradually worsened	benralizumab	effective for both asthma and complication

ECRS, eosinophilic chronic rhinosinusitis; EOM, eosinophilic otitis media; EGPA, eosinophilic granulomatosis with polyangiitis; BT, bronchial thermoplasty.

Credit authorship contribution statement

Tomohiro Akaba: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Mitsuko Kondo: Conceptualization, Writing – review & editing, Fumi Kobayashi: Investigation. Nahoko Honda: Methodology. Soshi Muramatsu: Writing – review & editing. Osamitsu Yagi: Conceptualization. Kiyoshi Takeyama: Formal analysis, Writing – review & editing. Yukako Seo: Conceptualization, Investigation. Manabu Nonaka: Supervision. Etsuko Tagaya: Supervision.

Declaration of competing interest

All authors have no conflicts of interest to declare in relation to this article.

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